AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (original) A method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution, which is used in preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more by dissolving a soluble thrombomodulin-containing freeze-dried preparation that contains soluble thrombomodulin as an active ingredient, the method being characterized by comprising at least one of:

(a) allowing the presence of at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol;

(b) an inner wall of a container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is coated with silicone; and

(c) a pressure in the container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is kept at a reduced pressure.

2. The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to claim 1, which is used in preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more by dissolving the soluble thrombomodulin-containing freeze-dried preparation,

the method being characterized by comprising allowing the presence of at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol.

3. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to claim 1 [[or 2]], characterized by allowing the presence of at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol in the soluble thrombomodulin-containing freeze-dried preparation.

4. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 3~~ claim 1, characterized by allowing the presence of at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol in a dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation.

5. ((currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 4~~ claim 1, characterized in that the inner wall of the container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is coated with silicone.

6. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 5~~ claim 1, characterized in that the pressure in the container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is kept at a reduced pressure.

7. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 6~~ claim 1, characterized in that the high-concentrated soluble thrombomodulin-containing

solution has a soluble thrombomodulin concentration of 17 mg/mL or more.

8. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 6~~ claim 1, characterized in that the high-concentrated soluble thrombomodulin-containing solution has a soluble thrombomodulin concentration of 25 mg/mL or more.

9. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 8~~ claim 1, characterized in that a fluid volume of the high-concentrated soluble thrombomodulin-containing solution prepared by dissolution is in a range of 0.1 mL to 2 mL and an osmotic pressure ratio upon dissolution thereof is in a range of 0.5 to 2.0.

10. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 9~~ claim 1, characterized in that the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain at least one combination selected from the group consisting of

(1) a combination containing two of glutamic acid or a salt thereof and mannitol,

(2) a combination containing two of glutamic acid or a salt thereof and lysine or a salt thereof,

(3) a combination containing two of glutamic acid or a salt thereof and asparaginic acid or a salt thereof, and

(4) a combination containing two of asparaginic acid or a salt thereof and mannitol; and

at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the soluble thrombomodulin-containing freeze-

dried preparation and/or at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation.

11. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 9~~ claim 1, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain any one of (1) urea or (2) urea and an amino acid; and at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and/or at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation.

12. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 8~~ claim 1, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain one or two compounds selected from the group consisting of arginine, glutamic acid, proline, serine, glycine, histidine, asparagine, lysine, phenylalanine, and valine, or salts thereof, trehalose, lactose, and sucrose; further, at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and/or at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the

dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation.

13. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 12~~ claim 1, characterized in that the nonionic surfactant comprises at least one compound selected from the group consisting of polyoxyethylene sorbitan fatty acid ester, polyoxyethylene/polyoxypropylene copolymer, polyoxyethylene alkylether, polyoxyethylene fatty acid ester, and polyoxyethylene hydrogenated castor oil.

14. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 13~~ claim 1, characterized in that the nonionic surfactant has an existential amount of 0.01 mg or more per 10 mg of the soluble thrombomodulin.

15. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 14~~ claim 1, characterized in that the soluble thrombomodulin comprises a peptide that can be dissolved in water in a concentration of 30 mg/mL or more.

16. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 15~~ claim 1, characterized in that the soluble thrombomodulin comprises a peptide containing one of the following sequences, has an action of promoting activation of protein C with thrombin, and can be dissolved in the absence of a surfactant:

i) an amino acid sequence at positions 19 to 132 of SEQ ID NO. 3 in a sequence listing;

ii) an amino acid sequence at positions 19 to 132 of SEQ ID NO. 7 in the sequence listing; and

iii) an amino acid sequence obtained by addition of, deletion of, or substitution with at least one amino acid in the amino acid sequence of the (i) or (ii).

17. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 15~~ claim 1, characterized in that the soluble thrombomodulin comprises a peptide encoded by DNA capable of hybridizing with complementary DNA having a base sequence corresponding to 55 to 396 of SEQ ID NO. 4 or 8 in the sequence listing under stringent conditions, has an action of promoting activation of protein C with thrombin, and can be dissolved in the absence of a surfactant.

18. (currently amended) The method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to ~~any one of claims 1 to 15~~ claim 1, characterized in that the soluble thrombomodulin comprises a peptide containing one of the following sequences, has an action of promoting activation of protein C with thrombin, and can be dissolved in the absence of a surfactant:

i) an amino acid sequence at positions 19 to 516 of SEQ ID NO. 1 in a sequence listing;

ii) an amino acid sequence at positions 19 to 516 of SEQ ID NO. 5 in the sequence listing; and

iii) an amino acid sequence obtained by addition of, deletion of, or substitution with at least one amino acid in the amino acid sequence of the (i) or (ii).

19. (original) A foam inhibitor for a high-concentrated soluble thrombomodulin-containing solution to be used in preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 20 mg/mL or more by dissolving a soluble thrombomodulin-containing freeze-dried preparation that contains soluble thrombomodulin as an active ingredient, the form

inhibitor comprising at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol as an active ingredient.

20. (original) A soluble thrombomodulin-containing freeze-dried preparation containing soluble thrombomodulin as an active ingredient or a kit preparation thereof which is a combination of the soluble thrombomodulin-containing freeze-dried preparation and a dissolving aqueous solution therefor, the soluble thrombomodulin-containing freeze-dried preparation being provided for preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more,

the soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof being characterized by at least one of

(a) that at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and/or at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the dissolving aqueous solution for the soluble thrombomodulin-containing freeze-dried preparation,

(b) that an inner wall of a container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is coated with silicone, and

(c) that a pressure in the container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is kept at a reduced pressure.

21. (original) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation of the soluble thrombomodulin-containing freeze-dried preparation and a dissolving aqueous solution therefor according to claim 20, the

soluble thrombomodulin-containing solution being provided for preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more, the soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof being characterized in that at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol and chlorobutanol is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation, and/or at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the dissolving aqueous solution for the soluble thrombomodulin-containing freeze-dried preparation.

22. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof according to claim 20 [[or 21]], characterized in that the high-concentrated soluble thrombomodulin-containing solution has a soluble thrombomodulin concentration of 25 mg/mL or more.

23. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation according to ~~any one of claims 20 to 22~~ claim 20, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain at least one combination selected from the group consisting of

(1) a combination containing two of glutamic acid or a salt thereof and mannitol,

(2) a combination containing two of glutamic acid or a salt thereof and lysine or a salt thereof,

(3) a combination containing two of glutamic acid or a salt thereof and asparaginic acid or a salt thereof, and

(4) a combination containing two of asparaginic acid or a salt thereof and mannitol; and

the soluble thrombomodulin-containing freeze-dried preparation can be dissolved in 0.1 mL to 2 mL of a dissolving aqueous solution to prepare a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more with an osmotic pressure ratio in a range of 0.5 to 2.0 upon dissolution thereof.

24. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation according to ~~any one of claims 20 to 22~~ claim 20, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain at least one combination selected from the group consisting of

(1) a combination containing two of glutamic acid or a salt thereof and mannitol,

(2) a combination containing two of glutamic acid or a salt thereof and lysine or a salt thereof,

(3) a combination containing two of glutamic acid or a salt thereof and asparaginic acid or a salt thereof, and

(4) a combination containing two of asparaginic acid or a salt thereof and mannitol; and

the soluble thrombomodulin-containing freeze-dried preparation can be dissolved in 0.1 mL to 2 mL of a dissolving aqueous solution to prepare a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more with an osmotic pressure ratio in a range of 0.5 to 2.0 upon dissolution thereof; and at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation.

25. (currently amended) The kit preparation of a soluble thrombomodulin-containing freeze-dried preparation according to ~~any one of claims 20 to 22~~ claim 20, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is

allowed to contain at least one combination selecting from the group consisting of

(1) a combination containing two of glutamic acid or a salt thereof and mannitol,

(2) a combination containing two of glutamic acid or a salt thereof and lysine or a salt thereof,

(3) a combination containing two of glutamic acid or a salt thereof and asparaginic acid or a salt thereof, and

(4) a combination containing two of asparaginic acid or a salt thereof and mannitol; and

the soluble thrombomodulin-containing freeze-dried preparation can be dissolved in 0.1 mL to 2 mL of dissolving aqueous solution to prepare a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more with an osmotic pressure ratio in a range of 0.5 to 2.0 upon dissolution thereof; and is characterized by at least one of

(a) that at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the dissolving aqueous solution for the soluble thrombomodulin-containing freeze-dried preparation,

(b) that an inner wall of a container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is coated with silicone, and

(c) that a pressure in the container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is kept at a reduced pressure.

26. (currently amended) The kit preparation of a soluble thrombomodulin-containing freeze-dried preparation according to ~~any one of claims 20 to 22~~ claim 20, characterized in that the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain at least one combination selected from the group consisting of

(1) a combination containing two of glutamic acid or a salt thereof and mannitol,
(2) a combination containing two of glutamic acid or a salt thereof and lysine or a salt thereof,
(3) a combination containing two of glutamic acid or a salt thereof and asparaginic acid or a salt thereof, and
(4) a combination containing two of asparaginic acid or a salt thereof and mannitol; and
that the soluble thrombomodulin-containing freeze-dried preparation can be dissolved in 0.1 mL to 2 mL of a dissolving aqueous solution to prepare a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more with an osmotic pressure ratio in a range of 0.5 to 2.0 upon dissolution thereof, and further characterized by at least one of
(a) that at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol is allowed to be present in the dissolving aqueous solution for the soluble thrombomodulin-containing freeze-dried preparation contains,
(b) that an inner wall of a container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is coated with silicone, and
(c) that a pressure in the container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is kept at a reduced pressure.

27. (currently amended) The kit preparation of a soluble thrombomodulin-containing freeze-dried preparation according to ~~any one of claims 20 to 22, 25, and 26~~ claim 20, characterized in that a fluid volume of the dissolving aqueous solution for the

soluble thrombomodulin-containing freeze-dried preparation is in a range of 0.1 mL to 2 mL and an osmotic pressure ratio upon dissolution thereof is in a range of 0.5 to 2.0.

28. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof according to ~~any one of claims 20 to 27~~ claim 20, characterized in that the soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof comprises a preparation for subcutaneous or intramuscular injection.

29. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof according to ~~any one of claims 20, 21, and 24 to 26~~ claim 20, characterized in that the nonionic surfactant comprises at least one compound selected from the group consisting of polyoxyethylene sorbitan fatty acid ester, polyoxyethylene/polyoxypropylene copolymer, polyoxyethylene alkylether, polyoxyethylene fatty acid ester, and polyoxyethylene hydrogenated castor oil.

30. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof according to ~~any one of claims 20, 21, 24 to 26, and 29~~ claim 20, characterized in that
the nonionic surfactant has an existential amount of 0.01 mg or more per 10 mg of the soluble thrombomodulin.

31. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof according to ~~any one of claims 20 to 30~~ claim 20, characterized in that the soluble thrombomodulin comprises a peptide that can be dissolved in water in a concentration of 30 mg/mL or more.

32. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof according to ~~any one of claims 20 to 31~~ claim 20, characterized in that the soluble thrombomodulin comprises a peptide containing one of the following sequences, has an action of promoting activation of protein C with thrombin, and can be dissolved in the absence of a surfactant:

i) an amino acid sequence at positions 19 to 132 of SEQ ID NO. 3 in a sequence listing;

ii) an amino acid sequence at positions 19 to 132 of SEQ ID NO. 7 in the sequence listing; and

iii) an amino acid sequence obtained by addition of, deletion of, or substitution with at least one amino acid in the amino acid sequence of the (i) or (ii).

33. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof according to ~~any one of claims 20 to 31~~ claim 20, characterized in that the soluble thrombomodulin comprises a peptide encoded by DNA capable of hybridizing with complementary DNA having a base sequence corresponding to 55 to 396 of SEQ ID NO. 4 or 8 in the sequence listing under stringent conditions, has an action of promoting activation of protein C with thrombin, and can be dissolved in the absence of a surfactant.

34. (currently amended) The soluble thrombomodulin-containing freeze-dried preparation or the kit preparation thereof according to ~~any one of claims 20 to 31~~ claim 20, characterized in that the soluble thrombomodulin comprises a peptide containing one of the following sequences, has an action of promoting activation of protein C with thrombin, and can be dissolved in the absence of a surfactant:

i) an amino acid sequence at positions 19 to 516 of SEQ ID NO. 1 in a sequence listing;

ii) an amino acid sequence at positions 19 to 516 of SEQ ID NO. 5 in the sequence listing; and

iii) an amino acid sequence obtained by addition of, deletion of, or substitution with at least one amino acid in the amino acid sequence of the (i) or (ii).

35. (original) A method of stabilizing soluble thrombomodulin in a soluble thrombomodulin-containing freeze-dried preparation that contains the soluble thrombomodulin as an active ingredient, characterized by comprising: allowing the soluble thrombomodulin-containing freeze-dried preparation to contain at lease one combination selected from the group consisting of

(1) a combination of two of glutamic acid or a salt thereof and mannitol,

(2) a combination of two of glutamic acid or a salt thereof and lysine or a salt thereof,

(3) a combination of two of glutamic acid or a salt thereof and asparaginic acid or a salt thereof, and

(4) a combination of two of asparaginic acid or a salt thereof and mannitol; and

dissolving the soluble thrombomodulin-containing freeze-dried preparation in 0.1 mL to 2 mL of a dissolving aqueous solution to prepare a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more with an osmotic pressure ratio in a range of 0.5 to 2.0 upon dissolution thereof.

36. (original) The method of stabilizing soluble thrombomodulin according to claim 35, characterized by further allowing the presence of a nonionic surfactant in the soluble thrombomodulin-containing freeze-dried preparation.

37. (original) The method of stabilizing soluble thrombomodulin according to claim 36, characterized in that the nonionic

surfactant is at least one compound selected from the group consisting of polyoxyethylene sorbitan fatty acid ester, polyoxyethylene/polyoxypropylene copolymer, polyoxyethylene alkylether, polyoxyethylene fatty acid ester, and polyoxyethylene hydrogenated castor oil.